BMS- 378806

Drug Class: **Microbicides**

Drug Description

BMS-378806, or BMS-806, is a small molecule entry inhibitor of HIV-1 that targets the viral envelope protein. [1] [2]

HIV/AIDS-Related Uses

BMS-378806 is being investigated for the treatment of subtype B HIV-1 infection, including both CCR5 and CXR4 strains.[3] BMS-378806 is also being investigated in vaginal administration formulations for the prevention of HIV-1 transmission when used in combination with other vaginal microbicides.[4]

Pharmacology

BMS-378806 targets viral entry by inhibiting the binding of HIV-1 gp120 to the CD4 receptor. The affinity of BMS-378806 for the gp120 molecule is similar to that of soluble CD4 cells, and binding occurs close to the CD4 cell-binding pocket.[5] Binding of gp120 is the first step of HIV infection at the cellular level; BMS-378806 appears to be the first compound to block this binding.[6]

BMS-378806 shows good oral bioavailability in animals and has low protein binding. It is active against viral strains with both the CCR5 and the CXCR4 coreceptors and is selective for HIV-1, specifically subtype B.[7] [8]

BMS-378806 retains activity against HIV strains resistant to protease inhibitors and reverse transcriptase inhibitors.[9] Resistance maps to substitutions located primarily near the CD4 binding sites of gp120, including A204D, F423Y, M434/I/V/T, and M475I. Other reported mutations include M475I, M434I/V, M426L, D350K, D185N, K655E, 1595F, V68A, and S440R.[10]

BMS-378806 has recently been tested as a topically administered vaginal microbicide in combination with other investigational entry inhibitors. BMS-378806 and CMPD 167 appear to be synergistic in vitro, inhibiting different stages of the viral-cell attachment and entry process.[11] When combined in vitro, CMPD167, C52L, and BMS-378806 inhibited infection of T cells and cervical tissue explants. Significant protection was achieved in macaques when BMS-378806 was used alone and in combination, even when applied up to 6 hours before challenge.[12] [13]

Adverse Events/Toxicity

BMS-378806 displayed an excellent safety profile in animal studies.[14] No significant cytotoxicity has been noted.[15]

Clinical Trials

For information on clinical trials that involve BMS-378806, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: BMS-378806 AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[16]

Topical.[17]

Dosage Form: Vaginal gel for topical use.[18]

Chemistry

CAS Name: Piperazine,

BMS- 378806

Chemistry (cont.)

CAS Number: 357263-13-9[20]

Molecular formula: C22-H22-N4-O4[21]

C65%,H5.4%,N13.8%,O15.8%[22]

Molecular weight: 406[23]

Other Names

BMS 378806[24]

BMS-806[25]

Further Reading

Lin, PR. A Small Molecule HIV-1 Inhibitor That Targets the HIV-1 Envelope and Inhibits CD4 Receptor Binding. Proc Natl Acad Sci USA 2003;100(19):11013-8.

Veazey RS, Klasse PJ, Schader SM, Hu Q, Ketas TJ, Lu M, Marx PA, Dufour J, Colonno RJ, Shattock RJ, Springer MS, Moore JP. Protection of macaques from vaginal SHIV challenge by vaginally delivered inhibitors of virus-cell fusion. Nature 2005 Nov 3;438(7064):99-102.

Manufacturer Information

BMS-378806
Bristol - Myers Squibb Co
PO Box 4500
Princeton, NJ 08543-4500
(800) 321-1335

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

References

1. AIDS - 2004;18:2325-41

2. Antivir Ther - 2002;7(Suppl 1):S6

3. AIDS - 2004;18:2325-41

4. Nature - 2005 Nov 3;428(7064):99-102

5. AIDS - 2004;18:2325-41

6. Proc Natl Acad Sci USA - 2003;100(19):11013-8

7. AIDS - 2004;18:2325-41

8. Proc Natl Acad Sci USA - 2003;100(19):11013-8

9. Antivir Ther - 2002;7(Suppl 1):S6

10. AIDS - 2004;18:2325-41

11. Nature - 2005 Nov 3;428(7064):99-102

12. Nature - 2005 Nov 3;428(7064):99-102

13. Bristol-Myers Squibb - Merck and Bristol-Myers Squibb License New AIDS Drugs to IPM for Development as Microbicides to Protect Women from HIV [press release], October 31, 2005. Available at: http://www.bms.com/news/press/data/fg_press_release_5975.html. Accessed 05/23/06.

14. Proc Natl Acad Sci USA - 2003;100(19):11013-8

15. Antivir Ther - 2002;7(Suppl 1):S6

16. Antivir Ther - 2002;7(Suppl 1):S6

17. Proc Natl Acad Sci USA - 2003;100(19):11013-8

18. Proc Natl Acad Sci USA - 2003;100(19):11013-8

19. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 05/23/06.

20. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 05/23/06.

21. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 05/23/06.

22. Calculation. -

23. Calculation. -

24. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 05/23/06.

25. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 05/23/06.